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Roth, Eli M.

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Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

[a] The Sterling Research Group, Cincinnati, OH, USA
[b] Cardiovascular Research Unit, Diabetes and Obesity Research Program, University of Helsinki, Finland
[c] Columbia University, New York, NY, USA
[d] Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
[e] Medical Research Institute, University of Dundee, Dundee, UK
[f] College of Public Health, University of Iowa, IA, USA
[g] Sanofi, Paris, France
[h] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[i] Sanofi, Montpellier, France

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ABSTRACT

Background: Efficacy and safety of alirocumab were compared with ezetimibe in hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy.
Methods: In a Phase 3, randomized, double-blind, double-dummy study (NCT01644474), patients (low-density lipoprotein cholesterol [LDL-C] 100–190 mg/dL, 10-year risk of fatal cardiovascular events ≥1%–<5% [systemic coronary risk estimation]) were randomized to ezetimibe 10 mg/day ($n = 51$) or alirocumab 75 mg subcutaneously (via 1-mL autoinjector) every 2 weeks (Q2W) ($n = 52$), with dose up-titrated to 150 mg Q2W (also 1 mL) at week 12 if week 8 LDL-C was ≥70 mg/dL. Primary endpoint was mean LDL-C % change from baseline to 24 weeks, analyzed using all available data (intent-to-treat approach, ITT). Analyses using on-treatment LDL-C values were also conducted.
Results: Mean (SD) baseline LDL-C levels were 141.1 (27.1) mg/dL (alirocumab) and 138.3 (24.5) mg/dL (ezetimibe). The 24-week treatment period was completed by 85% of alirocumab and 86% of ezetimibe patients. Least squares mean (SE) LDL-C reductions were 47 (3)% with alirocumab versus 16 (3)% with ezetimibe (ITT; $p < 0.0001$) and 54 (2)% versus 17 (2)% (on-treatment; $p < 0.0001$). At week 12, before up-titration, alirocumab 75 mg Q2W reduced LDL-C by 53 (2)% (on-treatment). Injection site reactions were infrequent (<2% and <4% of alirocumab and ezetimibe patients, respectively).
Conclusions: Alirocumab demonstrated significantly greater LDL-C lowering versus ezetimibe after 24 weeks with the lower 75 mg Q2W dose sufficient to provide ≥50% LDL-C reduction in the majority of the patients. Adverse events were comparable between groups.

Abbreviations: AE, adverse event; Apo, apolipoprotein; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; EOT, end of treatment; EZE, ezetimibe; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptors; LLN, lower limit of normal; Lp(a), lipoprotein (a); LS, least squares; mITT, modified intent-to-treat; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; NEC, not elsewhere classified; Non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin 9; Q2W, every 2 weeks; R, randomization; SAEs, serious adverse events; SC, subcutaneously; SCORE, systematic coronary risk estimation; SD, standard deviation; SE, standard error; TEAEs, treatment-emergent adverse events; TGs, triglycerides; ULN, upper limit of normal.

* Corresponding author at: Sterling Research Group 2230 Auburn Avenue Cincinnati, OH 45219, USA. Tel.: +1 513 381 4100; fax: +1 513 381 4120.
E-mail address: eroth@sterlingresearch.org (E.M. Roth).

1. Introduction

Alirocumab (formerly SAR236553/REGN727), a fully human monoclonal antibody against proprotein convertase subtilisin/kexin 9 (PCSK9), significantly reduced low-density lipoprotein cholesterol (LDL-C) when combined with other lipid-lowering therapies in three Phase 2 studies of 8–12 weeks duration [1–3]. Alirocumab Phase 2 clinical studies were all conducted with patients on background statin therapy [1–3]. Since statins increase PCSK9 levels, there is a need to also study alirocumab as monotherapy (i.e. with no background lipid-lowering therapies) to better understand the pharmacokinetics and

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pharmacodynamics of the drug, as well as its efficacy and safety, in patients not on statin therapy. Robust decreases in LDL-C were previously reported in a small number of patients treated with alirocumab as monotherapy [4].

We present data from the ODYSSEY MONO study, in the first report from the ODYSSEY program, a large series of Phase 3 studies designed to provide a comprehensive assessment of the efficacy and safety of alirocumab in a range of clinical settings and patient groups. The primary objective of this study was to evaluate the efficacy and safety of alirocumab monotherapy compared with ezetimibe in patients with hypercholesterolemia and at moderate cardiovascular (CV) risk (i.e. a 10-year risk of fatal CV events ≥1% and <5%) [5], who were not receiving statin or other lipid-lowering therapy. Ezetimibe was utilized as the comparator in this study as it is one of the options recommended for treating patients with statin intolerance [6]. The study employed a previously unstudied alirocumab dose regimen of 75 mg every 2 weeks (Q2W). The 75 mg Q2W dose was selected based on modeling data from the alirocumab Phase 2 trials [7].

2. Methods

This was a Phase 3, randomized, double-blind, active-controlled, double-dummy study (NCT01644474) conducted in eight centers in the USA, Belgium, Finland, and the Netherlands, from July 2012 to July 2013. The study was performed in accordance with the ethical principles in the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice and appropriate regulatory requirements. The study protocol was approved by the appropriate local independent ethics committees. Written, informed consent was received from all patients before enrollment.

2.1. Patients

This study included male and female patients aged ≥18 years with a 10-year risk of fatal CV events of ≥1% and <5%, based on the European Systematic Coronary Risk Estimation [5], a level of risk for which LDL-C lowering drug therapy can be considered [8]. Patients were not receiving statin or any other lipid-lowering therapy for at least 4 weeks prior to screening. Exclusion criteria are listed in Supplementary Table 1.

2.2. Study design

Patients were randomized (permuted-block design) in a 1:1 ratio to receive either ezetimibe 10 mg/day orally plus alirocumab placebo administered subcutaneously (SC) Q2W or alirocumab 75 mg SC Q2W plus ezetimibe oral placebo daily (Fig. 1). Alirocumab was administered using a 1-mL autoinjector; patients could self-inject or could designate another person to assist them if desired. Further details are given in the Supplementary methods.

Per protocol, patients in the alirocumab arm were to be up-titrated in a blinded manner to alirocumab 150 mg SC Q2W at week 12 if their week 8 LDL-C value was ≥100 mg/dL. However, due to an administrative error during the study, an up-titration threshold of 70 mg/dL instead of 100 mg/dL was utilized. Due to the double-blinded nature of the protocol, the error was not discovered until the data were analyzed after the study was complete.

2.3. Endpoints and assessments

The primary endpoint was the percent change from baseline in calculated LDL-C at 24 weeks with alirocumab compared with ezetimibe. Secondary endpoints are listed in Supplementary Table 2.

Safety was assessed throughout the study by adverse event (AE) reporting, local tolerability (injection site reactions), laboratory data, vital signs, physical signs, and electrocardiogram. Further details are given in the Supplementary methods. Treatment-emergent AEs (TEAEs) were defined as AEs that, irrespective of whether considered drug-related, developed or worsened or became serious during the TEAE period. The TEAE period was defined as the time from the first dose of study treatment to 70 days (10 weeks) after last injection, as residual effects of alirocumab were expected up to 10 weeks after last injection.

2.4. Statistical analyses

A sample size of 45 patients per treatment arm was calculated to have 95% power to detect a mean difference between alirocumab and ezetimibe of 20% in LDL-C percent change from baseline to week 24 using a 2-sided *t*-test with 5% significance, assuming a common standard deviation (SD) of 25% based on a previous alirocumab trial [1] and with an expected rate of exclusion of 5%. The primary endpoint was assessed in the intent-to-treat (ITT) population, which included all randomized patients who had at least one calculated LDL-C value at baseline and at one of the planned time points from weeks 4 to 24. A pre-specified on-treatment analysis (corresponding to the modified ITT or mITT) was also carried out which included all randomized and treated patients who had at least one calculated LDL-C value at baseline and at one of the planned time points from weeks 4 to 24 on-treatment, defined as the period between the first dose of study treatment and up to 21 days after last injection or 3 days after last capsule intake, whichever came first. Further details are given in the Supplementary methods.

3. Results

3.1. Patients

Of 204 patients screened, 103 met the eligibility criteria for the study and were randomized (52 to the alirocumab arm and 51 to the ezetimibe arm; Fig. 2). Baseline characteristics and lipid parameters were generally evenly distributed across the two study arms (Table 1). A total of four patients were identified as having diabetes mellitus at screening (three in the alirocumab arm and one in the ezetimibe arm). Mean baseline LDL-C levels were 141.1 mg/dL (3.65 mmol/L) in the alirocumab arm and 138.3 mg/dL (3.58 mmol/L) in the ezetimibe arm (Table 1).

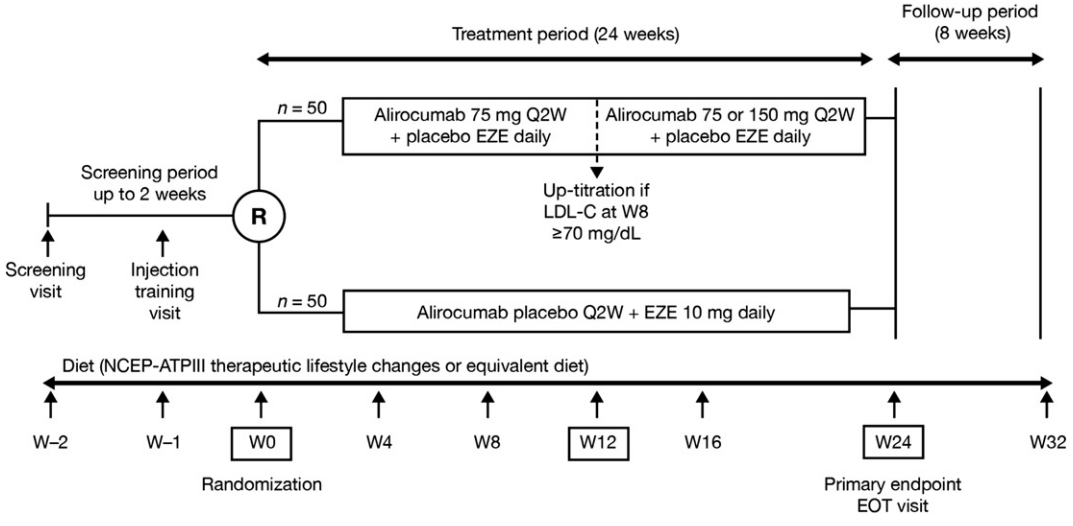

Fig 1. Study design.
Although the protocol called for an LDL-C threshold of ≥100 mg/dL for up-titration, a threshold of ≥70 mg/dL was applied in error in a blinded manner in this study. Arrows along the bottom of the figure indicate assessment times. EOT = end of treatment; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; Q2W = every 2 weeks; R = randomization; W = week.

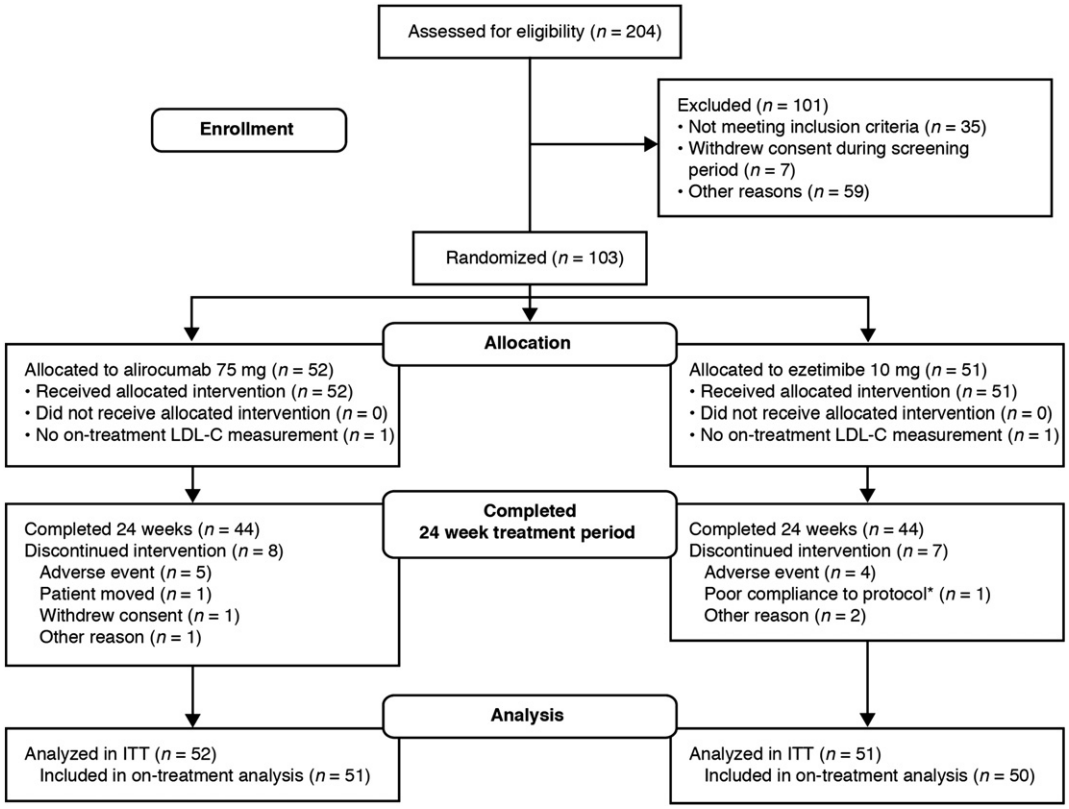

Fig 2. Patient disposition.
*Life events made continuing too difficult. ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol.

Fourteen patients in the alirocumab arm were up-titrated in a blinded manner at week 12 to the 150 mg Q2W dosing regimen because their week 8 LDL-C was ≥70 mg/dL; only one of these patients had LDL-C >100 mg/dL. Mean baseline LDL-C values were 153.2 mg/dL (3.96 mmol/L) in patients who were up-titrated to alirocumab 150 mg Q2W and 134.7 mg/dL (3.48 mmol/L) in patients who were not up-titrated. Baseline values of other lipid values according to whether patients were up-titrated or not are shown in Supplementary Table 3.

Overall, 44/52 (85%) patients in the alirocumab arm and 44/51 (86%) patients in the ezetimibe arm completed the 24-week treatment period (Fig. 2). The main reason for study treatment discontinuation in both treatment arms was TEAEs (Fig. 2). Of the 15 patients who prematurely

Table 1
Baseline characteristics (all randomized patients).

Characteristic (mean [SD] unless otherwise stated)	Alirocumab 75 mg Q2W (*N* = 52)	Ezetimibe 10 mg (*N* = 51)
Age, years	60.8 (4.6)	59.6 (5.3)
Male gender, *n* (%)	28 (53.8)	27 (52.9)
Race, *n* (%)		
White	46 (88.5)	47 (92.2)
Black or African American	6 (11.5)	4 (7.8)
BMI, kg/m^2	30.1 (5.9)	28.4 (6.7)
HbA1c, %	5.7 (0.5)	5.6 (0.4)
Fasting blood glucose, mg/dL	101.4 (14.3)	97.4 (9.0)
Diabetes mellitus, n (%)	3 (5.8)	1 (2.0)
10-Year risk of fatal CVD (SCORE), %	2.97 (1.29)	2.68 (1.14)
Lipid parameters, mg/dL		
LDL-C	141.1 (27.1)	138.3 (24.5)
Range (min:max)	77:207	73:186
Apolipoprotein B	104.3 (18.4)	104.3 (19.1)
Total cholesterol	221.7 (33.7)	223.9 (30.2)
Non-HDL-C	167.4 (30.3)	164.0 (29.7)
Lipoprotein (a), median (IQR)	13.0 (4.0:39.0)	16.0 (6.0:34.0)
Triglycerides, median (IQR)	119.0 (89.0:153.0)	117.0 (87.0:154.0)
HDL-C	54.3 (16.1)	59.9 (19.2)
Apolipoprotein A-1	153.1 (29.2)	163.8 (33.4)

There were no clinical or statistically significant between-group differences. To convert glucose measurements to mmol/L, multiply by 0.0555; to convert cholesterol measurements to mmol/L, multiply by 0.02586; and to convert triglycerides measurements to mmol/L, multiply by 0.01129. BMI = body mass index; CVD = cardiovascular disease; HbA1c = glycated hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks; SCORE = systemic coronary risk estimation; and SD = standard deviation.

discontinued treatment, three (6%) patients in the alirocumab arm and 5 (10%) patients in the ezetimibe arm did not have a calculated LDL-C value at week 24.

Forty-eight patients in each treatment group self-injected for all injections (92% in the alirocumab arm, 94% in the ezetimibe arm). Four patients in the alirocumab arm and three in the ezetimibe arm self-injected for some of the injections and requested another person to do so for the other injections. No patients asked another person to perform all their injections.

All randomized patients received at least one dose of their allocated drug and were included in the ITT and safety populations (Fig. 2). One patient from each treatment arm withdrew from treatment before any post-randomization LDL-C measurements were made and so were excluded from the on-treatment analysis. However, they continued the study and had LDL-C measurements taken while off-treatment but before end of the 24-week study period, so they were included in the ITT analysis.

3.2. Efficacy

For the primary efficacy analysis (ITT analysis), least-squares [LS] mean (standard error [SE]) percent reductions in LDL-C from baseline to week 24 were 47 (3)% in the alirocumab group versus 16 (3)% in the ezetimibe group, with a statistically significant LS mean (SE) difference between groups of −32 (4)% ($p < 0.0001$) (Table 2). Results from the on-treatment analysis were consistent with those from the ITT analysis: LS mean (SE) LDL-C reductions from baseline to week 24 were 54 (2)% versus 17 (2)% ($p < 0.0001$), with alirocumab and ezetimibe, respectively (Table 2).

At week 12, when all patients in the alirocumab arm were receiving 75 mg Q2W, LDL-C levels were reduced by 48 (3)% with alirocumab versus 20 (3)% with ezetimibe in the ITT analysis, with a between-group LS mean (SE) difference of −28 (4)% ($p < 0.0001$). Corresponding LDL-C reductions in the on-treatment analysis at week 12 were 53 (2)% with alirocumab versus 20 (2)% with ezetimibe, with a between-group LS mean (SE) difference of −33 (3)%.

Fig. 3 shows the time-course of changes in LDL-C levels over the study period for patients treated with alirocumab and ezetimibe. Here we have shown the on-treatment values since the purpose is to understand the durability of drug effect without any confounding by drop out. There was a substantial drop in LDL-C from baseline to week 4 in the patients who received alirocumab, with robust LDL-C reductions maintained from week 4 to end of the treatment period at week 24. Statistical analysis of the interaction between treatment and time point in the mixed model with repeated measures (see Supplemental methods) was not significant, suggesting stability of LDL-lowering effect of alirocumab versus ezetimibe over time (as illustrated in Fig. 3).

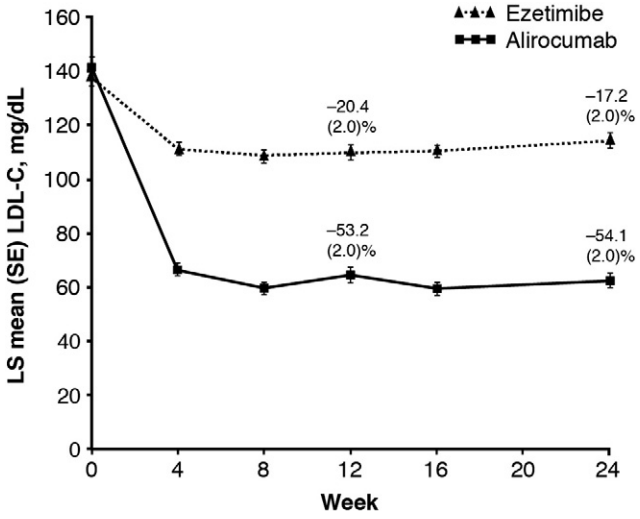

Fig 3. LDL-C levels (mg/dl) versus study time point (on-treatment analysis). Values above week 12 and week 24 data points indicate LS mean (SE) % change from baseline. LDL-C = low-density lipoprotein cholesterol; LS = least squares; SE = standard error.

The estimated proportions of patients with LDL-C reductions ≥50% at week 12, before up-titration, were 58% in the alirocumab arm, compared with 3% of patients in the ezetimibe arm (ITT). Corresponding values in the on-treatment analysis were 65% in the alirocumab arm and 2% in the ezetimibe arm. All patients responded to alirocumab while exposed to treatment (on-treatment population) (Supplemental Fig. 1).

To estimate the impact of the up-titration based on LDL-C ≥70 mg/dL instead of ≥100 mg/dL on the primary efficacy parameter, an additional analysis was performed excluding LDL-C values post up-titration for the 13 patients who were up-titrated despite having LDL-C values <100 mg/dL; this analysis gave results similar to the overall ITT analysis (Supplementary Table 4).

Percent reductions from baseline in apolipoprotein B, total cholesterol, and non-high density lipoprotein cholesterol were significantly greater for alirocumab versus ezetimibe at week 24 and similar in the ITT and on-treatment analyses (Table 3). Moderate reductions in lipoprotein (a) [Lp(a)], triglycerides and increases in high-density lipoprotein cholesterol were observed following both of the study treatments, with no significant differences between alirocumab and ezetimibe arms (Table 3).

Alirocumab efficacy versus ezetimibe was consistent across various subgroups in the ITT population (Supplementary Fig. 2).

Table 2
Percent change in LDL-C from baseline to week 24 (ITT and on-treatment analysis).

LDL-C	Alirocumab 75 mg Q2W	Ezetimibe 10 mg	Alirocumab versus ezetimibe		
			LS mean difference (SE) %	95% CI	*p*-Value
ITT	$N = 52$	$N = 51$			
LS mean (SE) change from baseline (%)	−47.2 (3.0)	−15.6 (3.1)	−31.6 (4.3)	−40.2 to −23.0	<0.0001[a]
On-treatment[b]	$N = 51$	$N = 50$			
Baseline LDL-C, mean (SD), mg/dL	141.1 (27.4)	137.5 (24.1)			
Min:max	77:207	73:186			
LS mean (SE) change from baseline (%)	−54.1 (2.0)	−17.2 (2.0)	−36.9 (2.9)	−42.7 to −31.2	<0.0001[c]

CI = confidence intervals; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LS = least squares; Q2W = every 2 weeks; SD = standard deviation; and SE = standard error.

[a] Statistically significant according to the fixed hierarchical approach used to control overall type-I error rate.

[b] Includes all patients in the ITT population with at least one calculated LDL-C value at one planned time point between the first dose of study treatment and up to 21 days after last injection or 3 days after last capsule intake, whichever came first.

[c] *p*-Value is shown for descriptive purposes only.

Table 3
Percent change from baseline in secondary lipid parameters (ITT and on-treatment analysis).

LS mean (SE) % change from baseline to week 24	Alirocumab 75 mg Q2W	Ezetimibe 10 mg	Alirocumab versus ezetimibe		
			LS mean difference (SE) %	95% CI	*p*-Value
ITT	*N* = 52	*N* = 51			
Apo B	−36.7 (2.3)	−11.0 (2.4)	−25.8 (3.3)	−32.3 to −19.2	<0.0001[a]
Non-HDL-C	−40.6 (2.8)	−15.1 (2.9)	−25.5 (4.1)	−33.5 to −17.4	<0.0001[a]
Total cholesterol	−29.6 (2.1)	−10.9 (2.2)	−18.7 (3.0)	−24.7 to −12.7	<0.0001[a]
Lp(a)[b]	−16.7 (3.7)	−12.3 (3.8)	−4.4 (5.3)	−14.8 to 5.9	0.4013
TGs[b]	−11.9 (4.2)	−10.8 (4.3)	−1.2 (5.9)	−12.7 to 10.3	0.8433[c]
HDL-C	6.0 (1.9)	1.6 (1.9)	4.4 (2.7)	−1.0 to 9.8	0.1116[c]
Apo A-1	4.7 (1.6)	−0.6 (1.6)	5.3 (2.2)	0.9 to 9.8	0.0196[c]
On-treatment	*N* = 51	*N* = 50			
Apo B	−40.8 (1.9)	−11.5 (1.9)	−29.2 (2.6)	−34.4 to −24.0	<0.0001[d]
Non-HDL-C	−47.1 (1.9)	−16.6 (1.9)	−30.5 (2.7)	−35.9 to −25.1	<0.0001[d]
Total cholesterol	−34.2 (1.6)	−12.0 (1.6)	−22.2 (2.3)	−26.7 to −17.7	<0.0001[d]
Lp(a)[b]	−17.7 (4.1)	−12.3 (4.0)	−5.4 (5.7)	−16.6 to 5.9	0.3506[d]
TGs[b]	−14.7 (4.4)	−12.7 (4.2)	−1.9 (6.0)	−13.7 to 9.8	0.7452[d]
HDL-C	8.0 (1.9)	1.7 (1.9)	6.2 (2.7)	0.8 to 11.6	0.0241[d]
Apo A-1	5.3 (1.6)	−0.7 (1.6)	6.1 (2.3)	1.6 to 10.6	0.0084[d]

Apo = apolipoprotein; CI = confidence intervals; HDL-C = high-density lipoprotein cholesterol; ITT = intention-to-treat; Lp(a) = lipoprotein (a); LS = least squares; Q2W = every 2 weeks; SE = standard error; and TGs = triglycerides.
[a] Statistically significant according to the fixed hierarchical approach used to control overall type-I error rate.
[b] Combined estimate for adjusted mean (SE) percent changes are shown for Lp(a) and TGs.
[c] As the difference in Lp(a) at week 24 was not significant for alirocumab versus ezetimibe, no further significance testing was performed as per the fixed hierarchical approach. *p*-Values for TGs, HDL-C and Apo A-1 are shown for descriptive purposes only.
[d] *p*-Values are shown for descriptive purposes only.

3.3. Safety

The overall percentage of patients who experienced at least one TEAE was 69% in the alirocumab arm and 78% in the ezetimibe arm (Table 4). There were no deaths. Two serious AEs (SAEs) were reported during the TEAE period: one patient, who had received alirocumab 75 mg Q2W for 3 months and had a history of atrial fibrillation and chronic obstructive pulmonary disorder, experienced a pulmonary embolism; study treatment was discontinued and the patient was hospitalized, where he recovered. One patient in the ezetimibe arm with a medical history of arthritis experienced glenoid erosion and was hospitalized for surgery (shoulder arthroplasty). The patient recovered in hospital and completed the study. Neither of the SAEs were considered by the investigator to be related to the study treatment. TEAEs occurring in 5% or more patients in either treatment arms are shown in Table 4.

Nine patients prematurely discontinued study treatment following one or more TEAEs (five [10%] patients in the alirocumab arm and four [8%] in the ezetimibe arm). In the alirocumab group, TEAEs leading to discontinuation were pulmonary embolism in one patient, nausea, fatigue, headache, and flushing in one patient, arthralgia (generalized aching) in one patient, injection site reaction in one patient, and diarrhea in one other patient. In the ezetimibe group, the TEAEs leading to discontinuation were gout in one patient, fatigue, back pain, and frequent urination in one patient, abdominal cramping and injection site reaction in one patient, and vivid dreams in one patient.

Muscle-related TEAEs occurred in two (4%) of alirocumab patients and two (4%) of ezetimibe patients. Elevated creatine kinase levels over 10 times the upper limit of normal were reported in one patient in the ezetimibe group (Table 4). Three patients experienced a local injection site reaction (one [2%] patient in the alirocumab group and two [4%] in the ezetimibe group). These events were of mild intensity. The patient in the alirocumab arm experienced three episodes of local injection site reaction following consecutive injections. Three patients who were treated with alirocumab 75 mg Q2W experienced at least one LDL-C value <25 mg/dL; no safety concern associated with the low LDL-C levels was observed with these three patients.

No patients in the alirocumab group and few (two or less) patients in the ezetimibe group presented abnormalities in vital signs (blood pressure, heart rate). In addition, there were no increases over three times the upper limit of normal in alanine aminotransferase or aspartate aminotransferase (Table 4). More patients had blood glucose ≥126 mg/dL (7 mmol/L) in the alirocumab arm than in the ezetimibe arm (six patients vs. one patient; Table 4). However, the six patients in the alirocumab arm who experienced high blood glucose during the treatment period had abnormal fasting glucose at screening or baseline and no pattern was observed in changes in either blood glucose or glycated hemoglobin A1c (HbA1c) from screening to week 24 (Supplementary Table 5).

Treatment emergent anti-drug antibodies were found in six (12%) patients in the alirocumab arm and were not observed in patients in the ezetimibe arm. Five of these patients were classified as having a persistent response with a positive anti-drug antibody status recorded at follow-up visit. For all anti-drug antibody-positive patients, titers were low and no neutralizing anti-drug antibody which may impact alirocumab pharmacokinetics, LDL-C effects, or safety was detected.

4. Discussion

This was the first Phase 3 study of alirocumab and the first to use the 75 mg Q2W dosing regimen. Alirocumab demonstrated superior efficacy in monotherapy compared with ezetimibe over 24 weeks of treatment. The reductions in LDL-C observed with alirocumab in this study suggests that, in these moderate CV risk patients who were not on background statin therapy, alirocumab 75 mg Q2W is sufficient to provide >50% LDL-C reduction in most patients. Results of the present study were generally in line with what was observed previously in alirocumab Phase 1 and 2 studies performed with or without background statin therapy [1–4]. The magnitude of LDL-C lowering of alirocumab monotherapy at the starting dose of 75 mg is similar to what can be achieved with high-intensity statins in monotherapy (50–55% for atorvastatin 80 mg or rosuvastatin 40 mg daily) [9–11]. In comparison, monotherapy with evolocumab, another monoclonal antibody to PCSK9, decreased measured LDL-C by 41–51% with doses 70–140 mg Q2W and by 39–48% with doses 280–420 mg every 4 weeks [12].

In the current study, patients were up-titrated to alirocumab 150 mg SC Q2W at week 12 if their week 8 LDL-C value was ≥70 mg/dL. While the alirocumab dose up-titration occurred at a lower LDL-C level than

Table 4
TEAEs and laboratory parameters (safety population).

AE category or laboratory parameter, *n* (%)	Alirocumab 75 mg Q2W ($n = 52$)	Ezetimibe 10 mg ($n = 51$)
Patients with any TEAE	36 (69.2)	40 (78.4)
Patients with any treatment emergent SAE	1 (1.9)	1 (2.0)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to treatment discontinuation	5 (9.6)	4 (7.8)
TEAEs occurring in ≥5% of patients in either group		
Nasopharyngitis	12 (23.1)	8 (15.7)
Diarrhea	6 (11.5)	2 (3.9)
Influenza	6 (11.5)	3 (5.9)
Arthralgia	3 (5.8)	2 (3.9)
Headaches	3 (5.8)	2 (3.9)
Nausea	3 (5.8)	3 (5.9)
Upper respiratory tract infection	2 (3.8)	5 (9.8)
Back pain[a]	1 (1.9)	3 (5.9)
Dizziness	1 (1.9)	3 (5.9)
Urinary tract infection	0	3 (5.9)
Patients with TEAEs of interest		
Musculoskeletal and connective tissue disorders	8 (15.4)	11 (21.6)
Muscle disorders	2 (3.8)	2 (3.9)
Myalgia	2 (3.8)	1 (2.0)
Muscle spasms	0	1 (2.0)
Musculoskeletal and connective tissue disorders NEC	2 (3.8)	5 (9.8)
Musculoskeletal pain	1 (1.9)	1 (2.0)
General disorders and administration site conditions	5 (9.6)	5 (9.8)
Injection site reaction	1 (1.9)	2 (3.9)
Laboratory parameters *n*/*N* (%)		
Alanine aminotransferase (ALT)		
≥3× ULN (if baseline ALT < ULN) or ≥2× the baseline value (if baseline ALT ≥ ULN)	0/52	0/51
>3× ULN	0/52	0/51
Aspartate aminotransferase		
>3× ULN	0/52	0/51
Glucose		
≤70 mg/dL (3.9 mmol/L) and <LLN	0/52	0/50
≥126 mg/dL (7 mmol/L) (fasted)	6/51 (11.8)[b]	1/50 (2.0)[b]
Albumin		
≤25 g/L	0/51	0/50
Creatine kinase		
>3× ULN	0/51	1/50 (2.0)
>10× ULN	0/51	1/50 (2.0)

TEAEs are AEs that developed or worsened or became serious during the TEAE period (defined as the time from the first dose of double-blind study treatment to the last injection plus 70 days [10 weeks], as residual effect of alirocumab was expected until 10 weeks after last injection). AE = adverse event; LLN = lower limit of normal; NEC = not elsewhere classified; Q2W = every 2 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event; and ULN = upper limit of normal.

[a] Back pain was also counted as a TEAE of special interest (musculoskeletal and connective tissue disorders NEC).

[b] The six alirocumab patients and the one ezetimibe patient with blood glucose ≥126 mg/dL (7 mmol/L) had abnormal fasting glucose at screening or baseline (and three of the six alirocumab patients were identified as having diabetes mellitus at screening); in these patients, no pattern was observed in changes of blood glucose over time (See Supplementary Table 6).

planned per protocol (i.e. ≥100 mg/dL), it is not anticipated that the LDL-lowering efficacy observed would have differed significantly if the up-titration had been performed at this threshold. In this and prior studies, the Friedewald method was used to calculate LDL-C concentrations as this is the method routinely used in clinical practice. While it is understood that calculated LDL-C does not give precise estimates at low LDL-C levels, only three patients in this study had calculated LDL-C levels below 25 mg/dL.

The magnitude of decrease in Lp(a) with alirocumab was expected based on Phase 2 studies where reductions in Lp(a) ranged from 13–35% with the 50–150 mg Q2W dose range [1–3]. The effect of ezetimibe on Lp(a) is not clear from the literature, with large variations between studies [13,14].

Alirocumab demonstrated tolerability and safety comparable with ezetimibe. This is an important observation, as ezetimibe is one of the options recommended for use in statin intolerant patients due to its favorable safety profile [6]. Safety results for alirocumab reflected those of previous Phase 2 trials, where alirocumab was administered on top of background statin with or without other lipid-lowering therapy [1–3].

To our knowledge, this study was the first blinded, randomized study to use an autoinjector to administer a monoclonal antibody to PCSK9, with the autoinjector used to deliver alirocumab doses of both 75 mg and 150 mg in 1 mL SC injections. All patients were able to self-inject with the autoinjector, with the majority of patients choosing to self-administer all alirocumab injections.

There were more patients with high blood glucose in the alirocumab arm than in the ezetimibe arm. However, all had abnormal fasting blood glucose levels at screening or baseline (based on the American Diabetes Association definition) [15], with no pattern observed in changes in either blood glucose or HbA1c over the course of the study. The number of patients was too small to draw any firm conclusions. A previous study reported that male mice over 4 months old with both copies of the *PCSK9* gene deleted, and thus no functional PCSK9 protein, had reduced insulin levels, increased blood glucose, and glucose intolerance [16]. However, these findings have not been observed in humans with *PCSK9* loss-of-function mutations including those with no functioning PCSK9 protein [17–19]. One genetic population study suggested that subjects with both a *PCSK9* R46L loss-of-function mutation and an *apoE3*/*E2* genotype show increased rates of insulin resistance [20]. No safety concerns related to glucose levels have been reported so far in trials of PCSK9 inhibitors, either with alirocumab [1–3] or evolocumab [21–23].

The number of patients included in the study was relatively small. However, the purpose of this study was to provide monotherapy data

to complement the range of data expected to emerge from the ODYSSEY Phase 3 clinical trial program, which has been designed to further assess the efficacy and safety of alirocumab, primarily when combined with statins. The program, comprising 14 studies of more than 23,500 patients and over 2000 study centers worldwide, will also evaluate alirocumab as monotherapy in a larger statin intolerant population (ODYSSEY ALTERNATIVE; NCT01709513), as well as assessing the effects of alirocumab in addition to statin therapy in a large CV outcomes trial (ODYSSEY OUTCOMES; NCT01663402).

To summarize, this is the first 6-month duration, Phase 3, blinded assessment of the PCSK9 inhibitor alirocumab. A reduction in LDL-C of 48% was observed in the alirocumab 75 mg Q2W arm at 12 weeks in a monotherapy population, versus 20% in the ezetimibe arm (ITT analysis). TEAEs occurred in 69.2% of alirocumab patients and 78.4% of ezetimibe patients. This was also the first randomized, controlled trial of an injectable monoclonal antibody to PCSK9 utilizing a disposable autoinjector, which resulted in a low rate of injection-related AEs (<2% of alirocumab and <4% ezetimibe patients). Alirocumab's superior efficacy and comparable safety with ezetimibe suggests it has the potential to be useful in clinical settings when an alternative to statin therapy is needed.

Conflict of interest

E.R. is employed by a company that has received research funds and has received consulting fees from Regeneron, Sanofi, and Amgen. M.-R.T. has been a consultant or has received honoraria from AstraZeneca, Kowa, Merck, Novartis, Sanofi-Aventis, and Pfizer. H.N.G. has received research support from Genzyme (Sanofi) and Sanofi-Regeneron, a consultant on an advisory board for Sanofi and Regeneron and has been a consultant for Amarin, Amgen, AstraZeneca, BristolMyersSquibb, GlaxoSmithKline, ISIS, Kowa, Merck, Novartis, and Pfizer. J.J.P.K. is a consultant to and has received honoraria from Sanofi, Regeneron, Omthera, AstraZeneca, Aegerion, Genzyme, Isis Pharmaceuticals, Roche, Pfizer, Eli Lilly, MSD, AtheroNova, Amgen, and Novartis. H.M.C. is a consultant or on an advisory panel for Pfizer, Sanofi Aventis, Regeneron, Novartis, and Eli Lilly, has received research support from Roche, Pfizer, Eli Lilly, Boehringer Ingelheim, and AstraZeneca, has participated in a lecture/speaker's bureau and received honorarium from Pfizer, and is a shareholder in Roche. J.G.R. is employed by a university that has received research funds from Amarin, Amgen, AstraZeneca, Daiichi-Sankyo, Esperion, Genentech/Hoffman La Roche, GlaxoSmithKline, Merck, Regeneron/Sanofi, Zinfandel/Takeda and is a consultant for Amgen, Pfizer, Sanofi and Regeneron. L.M. and M.B.-D. are employees of Sanofi. R.P. is an employee of Regeneron. This study was funded by Sanofi and Regeneron.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.06.049.

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